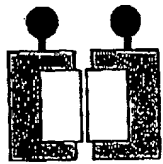
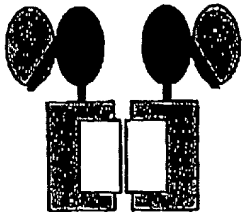


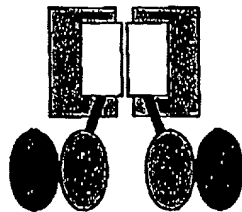
**Figure 1**



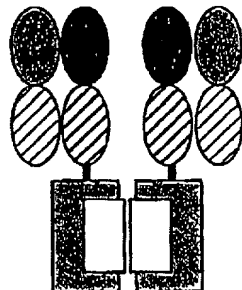
- (A) Small ligand-Caspase Hetero-tetramer (after N-terminal processing)



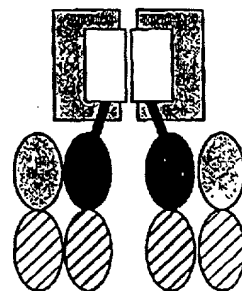
- (B) Single-chain Fv (VL-VH format)-Caspase Hetero-tetramer



- (C) Caspase Hetero-tetramer-Single-chain Fv (VL-VH format)

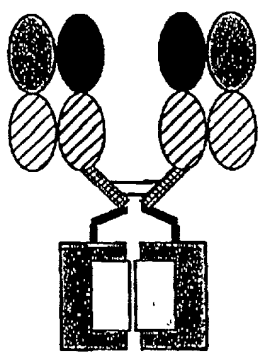


- (D) Fab-(Heavy chain fusion) Caspase Hetero-tetramer

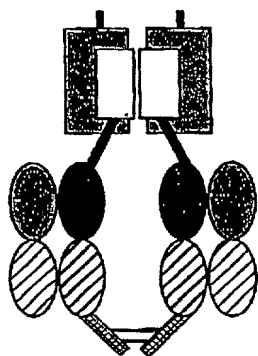


- (E) Caspase Hetero-tetramer Fab-(Heavy chain fusion)

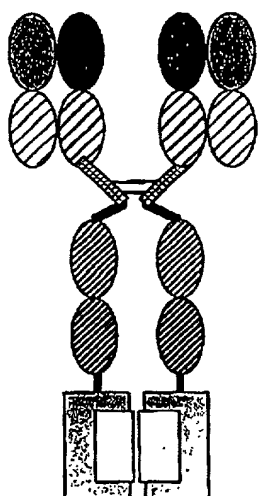
Figure 1 (cont)



(F) F(ab')<sub>2</sub>-Caspase heterotetramer  
Heavy chain fusion

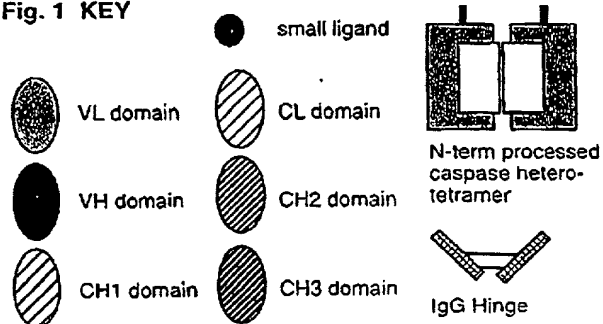


(G) Caspase heterotetramer-F(ab')<sub>2</sub>  
Heavy chain fusion



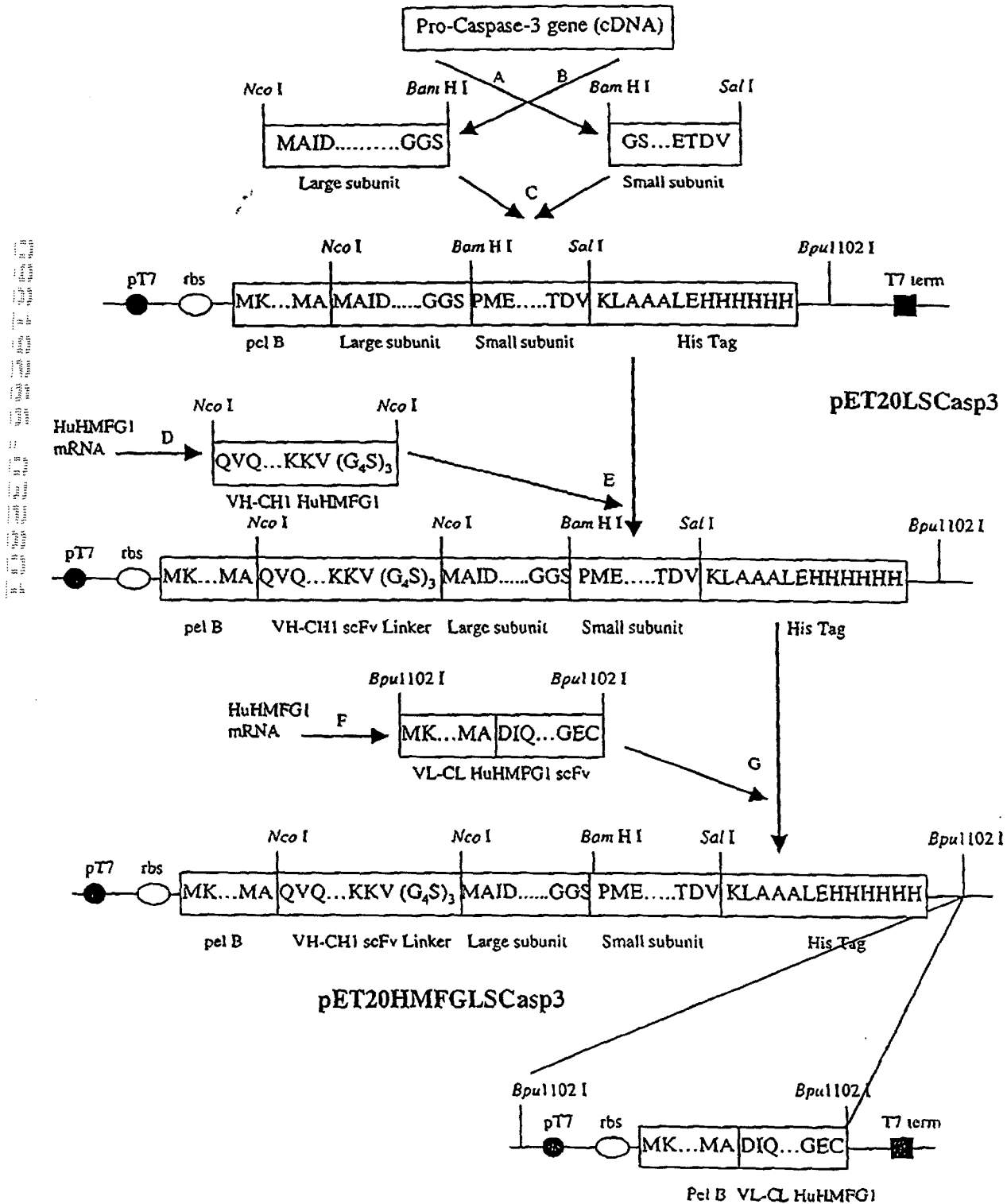
(H) IgG-Caspase heterotetramer

Fig. 1 KEY



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Figure 2



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Figure 3

1 60  
ATGAAATACCTATTGCCTACGGCAGCCGCTGGATTGTTATTACTCGCGGCCAGCCGGCC  
M K Y L L P T A A A G L L L L A A Q P A

61 120  
GCCAGGTGCAGCTGGTGCAGTCTGGGGCAGAGGTGAAAAGCCTGGGGCCTCAGTG  
M A Q V Q L V Q S G A E V K K P G A S V

121 180  
AAGGTGTCCTGCAAGGCTTCTGGCTACACCTTCAGTGCCTACTGGATAGAGTGGGTGCGC  
K V S C K A S G Y T F S A Y W I E W V R

181 240  
CAGGCTCCAGGAAAGGGCCTCGAGTGGGTCCGAGAGATTTTACCTGGAAGTAATAATTCT  
Q A P G K G L E W V G E I L P G S N N S

241 300  
AGATACAATGAGAAGTTCAAGGGCCGAGTGACAGTCACTAGAGACACATCCACAAACACA  
R Y N E K F K G R V T V T R D T S T N T

301 360  
GCCTACATGGAGCTCAGCAGCCTGAGGTCTGAGGACACAGCCGTCTATTACTGTGCAAGA  
A Y M E L S S L R S E D T A V Y Y C A R

361 420  
TCCTACGACTTTGCCTGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACAGTCTCCTCA  
S Y D F A W F A Y W G Q G T L V T V S S

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Figure 3 (cont)

421 480  
GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGG  
A S T K G P S V F P L A P S S K S T S G

481 540  
GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCG  
G T A A L G C L V K D Y F P E P V T V S

541 600  
TGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA  
W N S G A L T S G V H T F P A V L Q S S

601 660  
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACC  
G L Y S L S S V V T V P S S S L G T Q T

661 720  
TACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGGTGG  
Y I C N V N H K P S N T K V D K K V G G

Noted

721 780  
GGCGGTTCAAGCGGAGGTGGCTCTGGTGGAGGCGGTTCCATGGCGATCGATACAGACAGT  
G G S G G G S G G G S M A I D T D S

1261 1320  
GGTGTGATGATGACATGGCGTGTCAATAAATACCAAGTGGATGCCGACTTCTTGATGCA  
G V D D D M A C H K I P V D A D F L Y A

1321 1380  
TACTCCACAGCACCTGGTTATTATTCTTGGCGAAATTCAAAGGATGGCTCCTGGTTTCATC  
Y S T A P G Y Y S W R N S K D G S W F I

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Figure 3 (cont)

1381 1440  
CAGTCGCTTTGTGCCATGCTGAAACAGTATGCCGACAAGCTTGAATTTATGCACATTCTT  
Q S L C A M L K Q Y A D K L E F M H I L

1441 1500  
ACCCGGGTAAACCGAAAGGTGGCAACAGAATTTGAGTCCTTTTCCTTTGACGCTACTTTT  
T R V N R K V A T E F E S F S F D A T F

1501 1560  
CATGCAAAGAAACAGATTCCATGTATTGTTTCCATGCTCACAAAAGAACTCTATTTTTAT  
H A K K Q I P C I V S M L T K E L Y F Y

~~841 900~~  
~~TCCCTGGACAACAGTTATAAAATGGATTATCCTGAGATGGGTTTATGTATAATAATTAAT~~  
~~S L D N S Y K M D Y P E M G L C I I I N~~

1561 1620  
CACGATGAAGTTGATGGTGGATGCGCCGATGGAGAACACTGAAAACACTACGTGGATTCAAAA  
H D E V D G G S P M E N T E N S V D S K

781 840  
TCCATTAAAAATTTGGAACCAAAGATCATACATGGAAGCGAATCAATGGACTCTGGAATA  
S I K N L E P K I I H G S E S M D S G I

841 900  
TCCCTGGACAACAGTTATAAAATGGATTATCCTGAGATGGGTTTATGTATAATAATTAAT  
S L D N S Y K M D Y P E M G L C I I I N

901 960  
AATAAGAATTTTCATAAAAGCACTGGAATGACATCTCGGTCTGGTACAGATGTCGATGCA  
N K N F H K S T G M T S R S G T D V D A

961 1020  
GCAAACTCAGGGAAACATTCAGAAACTTGAAATATGAAGTCAGGAATAAAAAATGATCTT  
A N L R E T F R N L K Y E V R N K N D L

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Figure 3 (cont)

1021 1080  
ACACGTGAAGAAATTGTGGAATTGATGCGTGATGTTTCTAAAGAAGATCACAGCAAAGG  
T R E E I V E L M R D V S K E D H S K R

1081 1140  
AGCAGTTTTGTTTGTGTGCTTCTGAGCCATGGTGAAGAAGGAATAATTTTTGGAACAAAT  
S S F V C V L L S H G E E G I I F G T N

1141 1200  
GGACCTGTTGACCTGAAAAAATAACAACTTTTTTCAGAGGGGATCGTTGTAGAAGTCTA  
G P V D L K K I T N F F R G D R C R S L

1201 1260  
ACTGGAAAACCCAACTTTTCATTATTCAGGCCTGCCGTGGTACAGAACTGGACTGTGGC  
T G K P K L F I I Q A C R G T E L D C G

SalI

1261 1320  
ATTGAGACACAGGTCGACAAGCTTGC GGCCGCACTCGAGCACCACCACCACCACCTGA  
I E T D V D K L A A A L E H H H H H H \*

Bpu102I

1321 1380  
GATCCGGCTGCTAACAAAGCCCGAAAGGGCTGAGTTGGCTGCTGCCACCGCTGAGCGAAA

1381 1440  
TTAATACGACTCACTATAGGGAGACCACAACGGTTTCCCTCTAGAAATAATTTTGTTTAA

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Figure 3 (cont)

1441 1500

CTTTAAGAAGGAGATATACATATGAAATACCTATTGCCTACGGCAGCCGCTGGATTGTTA  
M K Y L L P T A A A G L L

1501 1560

TTACTCGCGGCCAGCCGGCAATGGCCGACATCCAGATGACCCAGAGCCCAAGCAGCCTG  
L L A A Q P A M A D I Q M T Q S P S S L

1561 1620

AGCGCCAGCGTGGGTGACAGAGTGACCATCACCTGTAAGTCCAGTCAGAGCCTTTTATAT  
S A S V G D R V T I T C K S S Q S L L Y

1621 1680

AGTAGCAATCAAAGATCTACTTGGCCTGGTACCAGCAGAAGCCAGGTAAGGCTCCAAAG  
S S N Q K I Y L A W Y Q Q K P G K A P K

1681 1740

CTGCTGATCTACTGGGCATCCACTAGGGAATCTGGTGTGCCAAGCAGATTCAGCGGTAGC  
L L I Y W A S T R E S G V P S R F S G S

1741 1800

GGTAGCGGTACCGACTTCACCTTCACCATCAGCAGCCTCCAGCCAGAGGACATCGCCACC  
G S G T D F T F T I S S L Q P E D I A T

1801 1860

TACTACTGCCAGCAATATTATAGATATCCTCGGACGTTCCGGCCAAGGGACCAAGGTGGAA  
Y Y C Q Q Y Y R Y P R T F G Q G T K V E

1861 1920

ATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG  
I K R T V A A P S V F I F P P S D E Q L



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Figure 3 (cont)

1921 1980  
AAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA  
K S G T A S V V C L L N N F Y P R E A K

1981 2040  
GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAG  
V Q W K V D N A L Q S G N S Q E S V T E

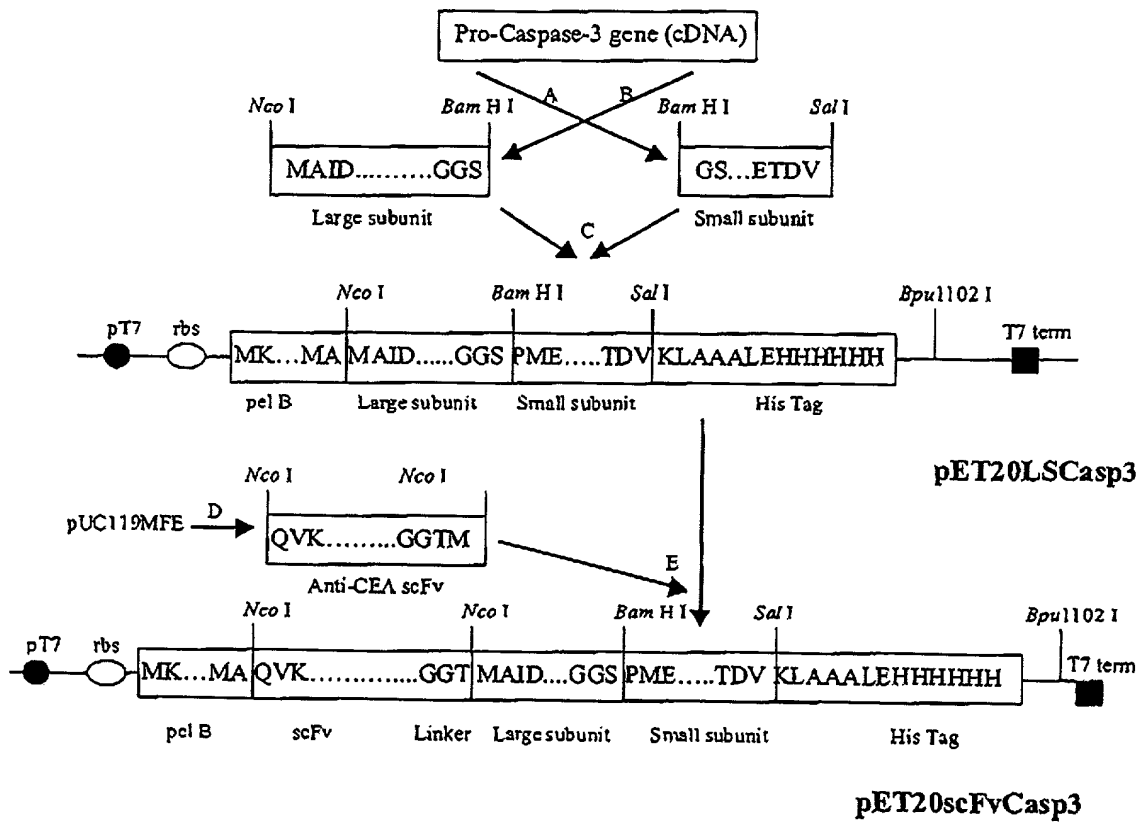
2041 2100  
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGAC  
Q D S K D S T Y S L S S T L T L S K A D

2101 2160  
TACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC  
Y E K H K V Y A C E V T H Q G L S S P V

2161 2206  
ACAAAGAGCTTCAACAGGGGAGAGTGTTAGTAGCAATGGGCTGAGC  
T K S F N R G E C \* \*

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Figure 4



**Figure 5**

10 20 30 40 50 60  
CCATGGGGCAGGTGAACTGCAGCAGTCTGGGGCAGAACTTGTGAGGTCAGGGACCTCAG  
GGTACCCCGTCCACTTTGACGTCGTCAGACCCCGTCTTGAACACTCCAGTCCCTGGAGTC  
M G Q V K L Q Q S G A E L V R S G T S

70 80 90 100 110 120  
TCAAGTTGTCCTGCACAGCTTCTGGCTTCAACATTAAAGACTCCTATATGCACTGGTTGA  
AGTTCAACAGGACGTGTCGAAGACCGAAGTTGTAATTTCTGAGGATATACGTGACCAACT  
V K L S C T A S G F N I K D S Y M H W L

130 140 150 160 170 180  
GGCAGGGGCCTGAACAGGGCCTGGAGTGGATTGGATTGATCCTGAGAATGGTGATA  
CCGTCCCCGGACTTGTCCCGGACCTCACCTAACCTACCTAAGGACTCTTACCACTAT  
R Q G P E Q G L E W I G W I D P E N G D

190 200 210 220 230 240  
CTGAATATGCCCCGAAGTTCCAGGGCAAGGCCACTTTTACTACAGACACATCCTCCAACA  
GACTTATACGGGGCTTCAAGGTCCCGTTCCGGTGAAAATGATGTCTGTGTAGGAGGTTGT  
T E Y A P K F Q G K A T F T T D T S S N

250 260 270 280 290 300  
CAGCCTACCTGCAGCTCAGCAGCCTGACATCTGAGGACACTGCCGTCTATTATTGTAATG  
GTCGGATGGACGTCGAGTCGTCGGACTGTAGACTCCTGTGACGGCAGATAATAACATTAC  
T A Y L Q L S S L T S E D T A V Y Y C N

**Figure 5 (cont)**

310 320 330 340 350 360  
AGGGGACTCCGACTGGGCCGTACTACTTTGACTACTGGGGCCAAGGGACCACGGTCACCG  
TCCCCTGAGGCTGACCCGGCATGATGAAACTGATGACCCCGGTTCCCTGGTGCCAGTGGC  
E G T P T G P Y Y F D Y W G Q G T T V T

370 380 390 400 410 420  
TCTCCTCAGGTGGAGGCGGTTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGATCAGAAAATG  
AGAGGAGTCCACCTCCGCCAAGTCCGCCTCCACCGAGACCGCCACCGCCTAGTCTTTTAC  
V S S G G G S G G G G S G G G G S E N

430 440 450 460 470 480  
TGCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCATAACCT  
ACGAGTGGGTCAGAGGTCGTTAGTACAGACGTAGAGGTCCCCTCTTCCAGTGGTATTGGA  
V L T Q S P A I M S A S P G E K V T I T

490 500 510 520 530 540  
GCAGTGCCAGCTCAAGTGTAAGTTACATGCACTGGTTCCAGCAGAAGCCAGGCACTTCTC  
CGTCACGGTCGAGTTCACATTCAATGTACGTGACCAAGGTCGTCTTCGGTCCGTGAAGAG  
C S A S S S V S Y M H W F Q Q K P G T S

550 560 570 580 590 600  
CCAAACTCTGGATTTATAGCACATCCAACCTGGCTTCTGGAGTCCCTGCTCGCTTCAGTG  
GGTTTGAGACCTAAATATCGTGTAGGTTGGACCGAAGACCTCAGGGACGAGCGAAGTCAC  
P K L W I Y S T S N L A S G V P A R F S

**Figure 5 (cont)**

610            620            630            640            650            660  
GCAGTGGATCTGGGACCTCTTACTCTCTCACAATCAGCCGAATGGAGGCTGAAGATGCTG  
CGTCACCTAGACCCTGGAGAATGAGAGAGTGTTAGTCGGCTTACCTCCGACTTCTACGAC  
G S G S G T S Y S L T I S R M E A E D A

670            680            690            700            710            720  
CCACTTATTACTGCCAGCAAAGGAGTAGTTACCCACTCACGTTCCGGTGCTGGCACCAAGC  
GGTGAATAATGACGGTCGTTTTCCTCATCAATGGGTGAGTGCAAGCCACGACCGTGGTTCG  
A T Y Y C Q Q R S S Y P L T F G A G T K

730            740            750            760            770            780  
TGGAGCTGCAACCGGGAGGTTCTGGAGGAACCATGGCGATCGATACAGACAGTGGTGTTG  
ACCTCGACGTTGGCCCTCCAAGACCTCCTTGGTACCGCTAGCTATGTCTGTCACCACAAC  
L E L Q P G G S G G T M A I D T D S G V

790            800            810            820            830            840  
ATGATGACATGGCGTGTCATAAAATACCAGTGGATGCCGACTTCTTGTATGCATACTCCA  
TACTACTGTACCGCACAGTATTTTATGGTCACCTACGGCTGAAGAACATACGTATGAGGT  
D D D M A C H K I P V D A D F L Y A Y S

850            860            870            880            890            900  
CAGCACCTGGTTATTATTCTTGGCGAAATTCAAAGGATGGCTCCTGGTTCATCCAGTCGC  
GTCGTGGACCAATAATAAGAACCGCTTTAAGTTTCCTACCGAGGACCAAGTAGGTCAGCG  
T A P G Y Y S W R N S K D G S W F I Q S

**Figure 5 (cont)**

910 920 930 940 950 960  
TTTGTGCCATGCTGAAACAGTATGCCGACAAGCTTGAATTTATGCACATTCTTACCCGGG  
AAACACGGTACGACTTTGTCATACGGCTGTTCGAACTTAAATACGTGTAAGAATGGGCCC  
L C A M L K Q Y A D K L E F M H I L T R

970 980 990 1000 1010 1020  
TTAACCGAAAGGTGGCAACAGAATTTGAGTCCTTTTCCTTTGACGCTACTTTTCATGCAA  
AATTGGCTTTCCACCGTTGTCTTAAACTCAGGAAAAGGAACTGCGATGAAAAGTACGTT  
V N R K V A T E F E S F S F D A T F H A

1030 1040 1050 1060 1070 1080  
AGAAACAGATTCCATGTATTGTTTCCATGCTCACAAAAGAACTCTATTTTTATCACGATG  
TCTTTGTCTAAGGTACATAACAAAGGTACGAGTGTTTTCTTGAGATAAAAATAGTGCTAC  
K K Q I P C I V S M L T K E L Y F Y H D

1090 1100 1110 1120 1130 1140  
AAGTTGATGGTGGATCCCCGATGGAGAACACTGAAAACCTACGTGGATTCAAATCCATTA  
TTCAACTACCACCTAGGGGCTACCTCTTGTGACTTTTGATGCACCTAAGTTTTAGGTAAT  
E V D G G S P M E N T E N Y V D S K S I

1150 1160 1170 1180 1190 1200  
AAAATTTGGAACCAAAGATCATACATGGAAGCGAATCAATGGACTCTGGAATATCCCTGG  
TTTTAAACCTTGGTTTCTAGTATGTACCTTCGCTTAGTTACCTGAGACCTTATAGGGACC  
K N L E P K I I H G S E S M D S G I S L

## Figure 5 (cont)

1210 1220 1230 1240 1250 1260  
ACAACAGTTATAAAATGGATTATCCTGAGATGGGTTTATGTATAATAATTAATAATAAGA  
TGTTGTCAATATTTTACCTAATAGGACTCTACCCAAATACATATTATTAATTATTATTCT  
D N S Y K M D Y P E M G L C I I I N N K

1270 1280 1290 1300 1310 1320  
ATTTTCATAAAAGCACTGGAATGACATCTCGGTCTGGTACAGATGTCGATGCAGCAAACC  
TAAAAGTATTTTCGTGACCTTACTGTAGAGCCAGACCATGTCTACAGCTACGTCGTTTGG  
N F H K S T G M T S R S G T D V D A A N

1330 1340 1350 1360 1370 1380  
TCAGGGAAACATTTCAGAACTTGAAATATGAAGTCAGGAATAAAAATGATCTTACACGTG  
AGTCCCTTTGTAAGTCTTTGAACTTTTATACTTCAGTCCTTATTTTACTAGAATGTGCAC  
L R E T F R N L K Y E V R N K N D L T R

1390 1400 1410 1420 1430 1440  
AAGAAATTGTGGAATTGATGCGTGATGTTTCTAAAGAAGATCACAGCAAAGGAGCAGTT  
TTCTTTAACACCTTAACTACGCACTACAAAGATTTCTTCTAGTGTGCTTTTCCTCGTCAA  
E E I V E L M R D V S K E D H S K R S S

1450 1460 1470 1480 1490 1500  
TTGTTTGTGTGCTTCTGAGCCATGGTGAAGAAGGAATAATTTTGGAAACAAATGGACCTG  
AACAAACACACGAAGACTCGGTACCACTTCTTCCTTATTA AAAACCTTGTTTACCTGGAC  
F V C V L L S H G E E G I I F G T N G P

1570            1580            1590            1600            1610            1620

AACCCAAACTTTTTCATTATTCAGGCCTGCCGTGGTACAGAACTGGACTGTGGCATTGAGA

TTGGGTTTGAAAAGTAATAAGTCCGGACGGCACCATGTCTTGACCTGACACCGTAACTCT

K   P   K   L   F   I   I   Q   A   C   R   G   T   E   L   D   C   G   I   E

1630            1640            1650            1660            1670  
 CACAGGTCGACAAGCTTGCGGCCGCACTCGAGCACCACCACCACCACCCTGA  
 GTGTCCAGCTGTTTGAACGCCGGCGTGAGCTCGTGGTGGTGGTGGTGGTACT  
 T   Q   V   D   K   L   A   A   A   L   E   H   H   H   H   H   H   \*



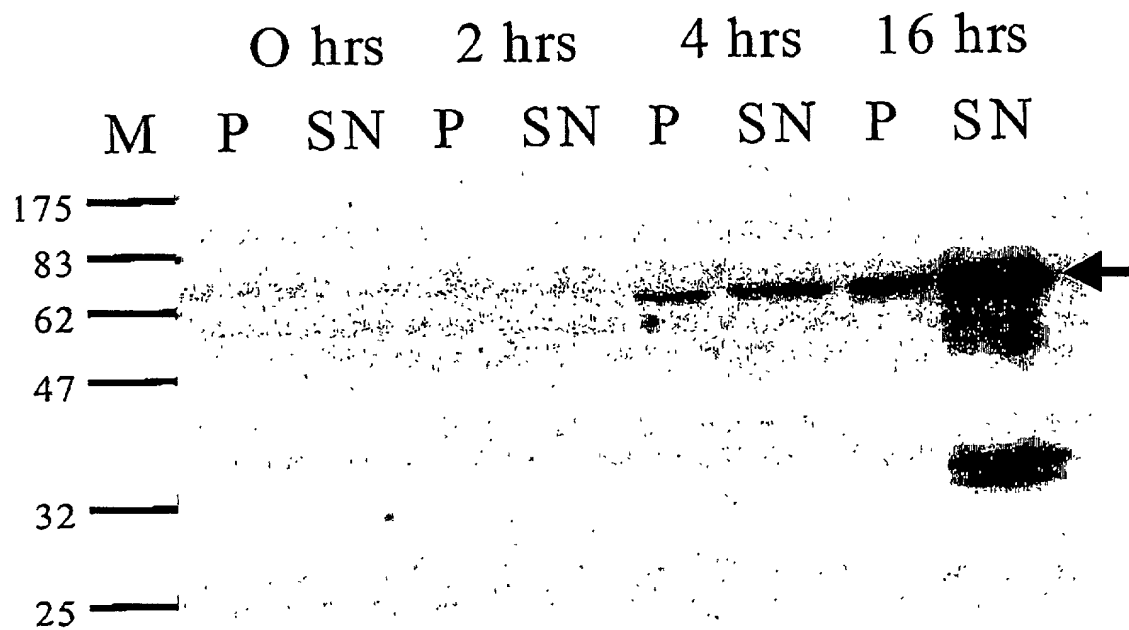
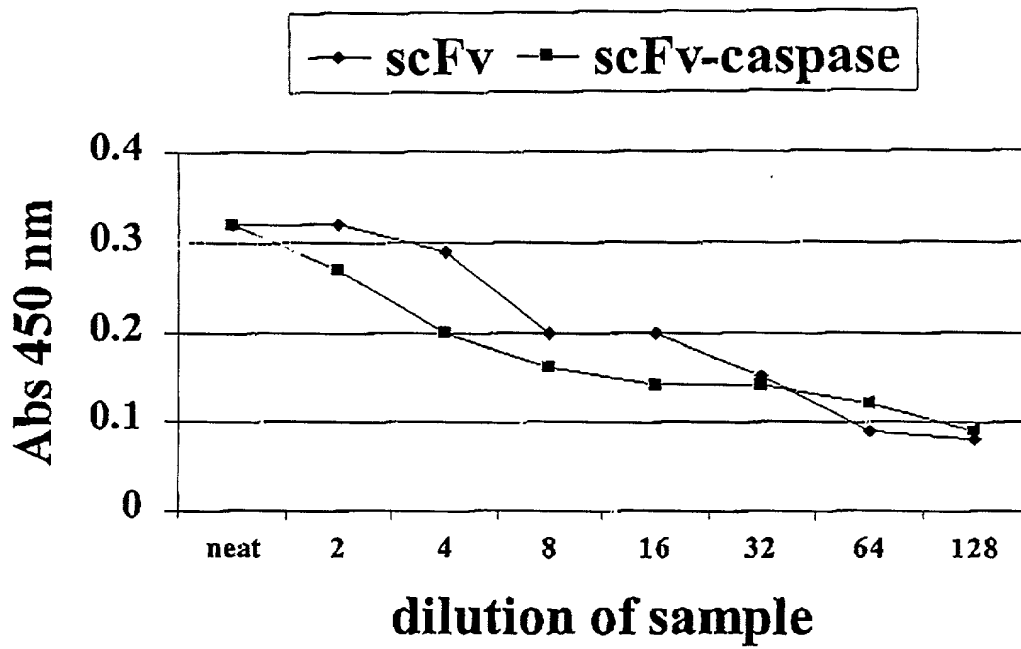
**Figure 6**

Figure 7



**Figure 8**

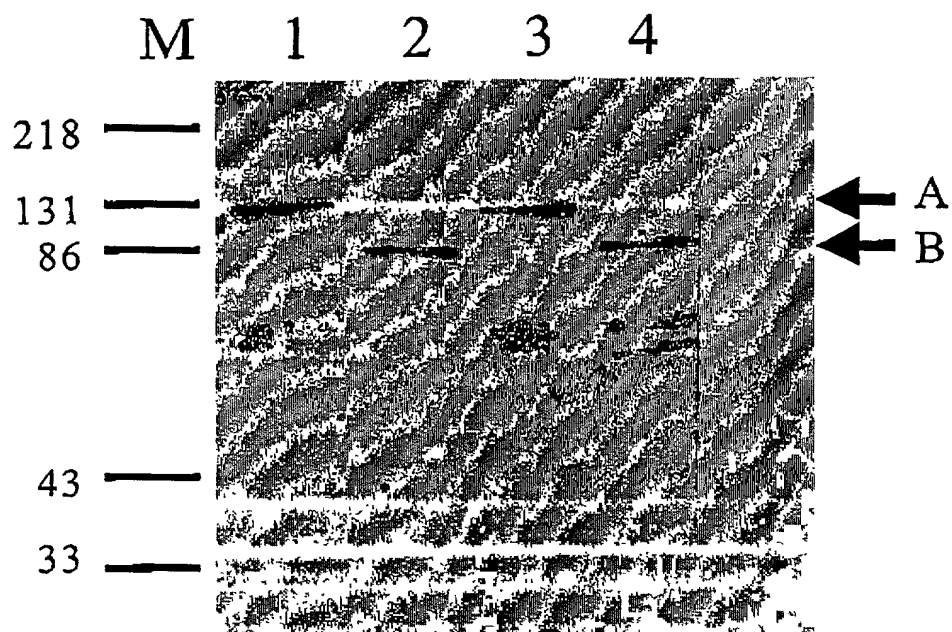


Figure 9

